Role of Poly (ADP-Ribose) Polymerase inhibitors beyond BReast CAncer Gene-mutated ovarian tumours: definition of homologous recombination deficiency?

Role of PARP inhibitors beyond BRCA mutated ovarian tumours; definition of homologous recombination deficiency?

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Abstract

Purpose of review: PARP inhibitors have transformed the management of BRCA mutant ($BRCA^{mut}$) high-grade serous and endometroid ovarian cancer (HGOC). However, it is clear the benefit can be extended beyond this subgroup, particularly to those cancers with homologous recombination repair deficiency (HRD). We review emerging molecular and clinical data to support the use of PARP inhibitors in HRD HGOC and discuss the advantages and disadvantages of different HRD assays.

Recent Findings: Several phase 3 trials support the use of PARP inhibitor maintenance therapy beyond those patients with $BRCA^{mut}$ in the first-line and platinum sensitive relapse setting. Many of these studies included HRD testing and it is clear, regardless of the assay used, that an incremental reduction in benefit is observed from $BRCA^{mut}$ tumours to HRD to homologous recombination proficient tumours. However, whilst currently available HRD assays predict the magnitude of benefit from PARP inhibitors, they consistently fail to identify a sub-group of patients who do not benefit.

Summary: Clinical data supports the use of PARP inhibitor maintenance therapy beyond $BRCA^{mut}$ patients. Current HRD tests lack negative predictive value and more research is required to develop a composite HRD assay which provides a dynamic readout of HRD status.

Keywords: Ovarian cancer, PARP inhibitors, BRCA, homologous recombination deficiency (HRD)

Introduction

PARP inhibitors represent the biggest breakthrough in the systemic treatment of the most common and most lethal forms of ovarian cancer (high grade serous and endometroid, HGOC) in the last 20 years. In patients whose tumours harbour a *BRCA1* or *BRCA2* mutation (*BRCA*^{mut}), PARP inhibitor maintenance therapy produces an unprecedented progression free survival (PFS) benefit in the first-line and relapsed disease settings (1-5). PARP inhibitor use can even result in long term (>6 year) remission for some patients with relapsed disease (6). The key to this sensitivity is believed to be the homologous recombination deficiency (HRD) which is typified by the lack of a functional copy of either *BRCA1* or *BRCA2*. However, the BRCA genes can by inactivated by non-mutational processes and there are many other proteins involved in homologous recombination repair (HRR) whose loss can also confer an HRD phenotype. PARP inhibitor studies in patients whose tumours do not harbour a *BRCA*^{mut} also demonstrate evidence of significant efficacy (2, 4, 7-10) but strategies for accurate patient selection remain elusive. In this review we discuss from the molecular and clinical perspectives the importance of homologous recombination repair in ovarian cancer, the advantages and disadvantages of the various HRD assays and additional factors that contribute to the assessment of HRD in patients being considered for PARP inhibitor therapy.

Homologous recombination repair (HRR)

HRR is a process conserved in evolution from bacteria to humans which facilitates the exchange of genetic information and within the cancer context allows the repair of breaks in double stranded DNA with the use of a template, thus maintaining the integrity of the sequence. Some of the key genes which when disrupted or dysregulated result in homologous recombination deficiency are shown in Figure 1. These include: *BRCA1* and *BRCA2*; genes that are less commonly disrupted but still responsible for hereditary cancer such as *BARD1*, *BRIP1* and *PALB2*; (11, 12) RAD family genes; (11-13) HR-related genes such as *EMSY*, *CHEK1* or *CHEK2*; (11-13) genes involved in activating the DNA damage response such as ATM, ATR and ATX; (11, 13) and the Fanconi anaemia genes (13).

The efficacy of PARP inhibitors is primarily related to their ability to trap PARP on DNA strands. When replication forks meet trapped PARP they stall and in the absence of functional HRR they collapse (14). This results in double-stranded DNA breaks which in HRD cells have to be dealt with by error-prone DNA repair mechanisms such as non-homologous end-joining or microhomology-mediated repair (15).

Homologous recombination deficiency in ovarian cancer

The reason why PARP inhibition has been particularly successful in HGOC relates to the biology of this disease. Rather than being characterised by oncogene activation, HGOC has almost ubiquitous *TP53* mutation (16), which in turn allows the cancer cells to tolerate DNA repair deficiencies, copy number abnormalities and multiple large chromosomal structural variants (Figure 2) (17) without undergoing cell cycle arrest or apoptosis. Indeed, approximately half of all HGOCs have molecular aberrations which have the potential to confer HRD (Figure 2). Germline and somatic *BRCA*^{mut} when combined account for almost half of these HRD HGOC cases. The rest are made up by methylation of *BRCA1* and *RAD51C*, amplification or overexpression of EMSY and non-BRCA HR gene mutations. Similarly, although case numbers are smaller, there is a suggestion from clinical studies that RAD51C methylation confers PARP inhibitor sensitivity (18) but the role of EMSY in HRD is less clear (19). The remaining small percentage of HRD HGOC cases are made up of mutations in minor HR genes, RAD family genes, HR related genes, DNA damage response genes and Fanconi anaemia genes outlined in Figure 1.

Strategies to determine HRD status in *BRCA* wild-type tumours

Strategies to select HGOC patients with *BRCA*^{wt} tumours who are most likely to benefit from PARP inhibition can be grouped into four main categories: clinical; functional; sequence/epigenetic and DNA 'scarring' assays.

Clinical selection of patients who had responded to multiple lines of platinum-based chemotherapy was utilised in relapsed disease PARP inhibitor studies on the basis that HRD confers platinum sensitivity for similar biological reasons that allow it to confer PARP inhibitor sensitivity. However, multiple *in vitro* and *in vivo* studies have demonstrated that the overlap between PARP inhibitor and platinum resistance is incomplete and vice versa (20-22).

Functional assays rely upon assessing whether cells have the capacity for HRR. In theory this is an excellent strategy because it determines the actual HRD status of the cells at that point in time rather than a molecular change or a genomic scar either of which could have been subsequently rendered irrelevant by mechanisms of resistance. The assays utilised to date have been cumbersome, requiring *in vitro* culture of tumour cells followed by assessment for gammaH2AX and Rad51 focus formation following PARP inhibitor exposure. However, they have demonstrated promise in terms of capacity to determine PARP inhibitor sensitivity (23). A recent study performing the RAD51 assessment in formalin fixed paraffin embedded material suggests that this may be more predictive of PARP inhibitor sensitivity than sequencing, epigenetic studies and scarring assays (24).

Although sequencing to detect genetic mutations or epigenetic changes in HRD genes can easily be done, it has become clear that some patients with HGOC have a good response to PARP inhibitors with no discernible mutational event (25, 26). This suggests there are some HRD mechanisms that we cannot presently explain.

Genomic scarring assays, like functional assays do not require an understanding of the underlying molecular cause of the HRD, they simply detect that it exists. The commercial assays that have been primarily used in ovarian cancer studies to date are the Foundation Medicine loss of heterozygosity (LOH) assay (2, 18, 26) and the Myriad MyChoice assay (4, 7, 8, 10, 26). These assays generate a score based upon the extent of LOH (Foundation Medicine) or a combination of LOH, large scale transitions and telomeric imbalance (Myriad MyChoice). The benefit of these assays is that they cover a variety of molecular causes of HRD. The disadvantage is that they only determine that there was HRD present at some point in time, and not necessarily that it is currently present. For example, if the tumour cell was initially HRD but developed a resistance mechanism restoring HRR, the same score from the genomic scarring assays would be obtained and the restoration would not be detectable (false positive issue). In addition, it is clear from some of the key PARP inhibitor clinical trials that there are patients who are homologous recombination proficient (HRP) by the scarring assays and yet benefit from PARP inhibition (false negative issue) (2, 4, 8).

Although a full discussion of the mechanisms of PARP inhibitor resistance are beyond the scope of this review (comprehensively outlined by Mateo et al) (27), it is clear that a better understanding of these is key to improving our selection of patients for PARP inhibitor therapy. The resistance mechanisms can be separated into two main groups. The first involves changes that restore HRR, either through re-expression of a gene that was mutationally or epigenetically silenced or through rewiring of the DNA damage response. In these cases, sequencing of archival material or scarring assays could be misleading if the resistance event is not detected. The second group of resistance mechanisms do not result in restoration of HRR and includes processes such as reduction in PARP trapping, (28, 29) replication fork protection (30, 31) and increased drug efflux (22).

Clinical evidence for efficacy beyond BRCA

Recurrent disease

The initial phase I/II studies with olaparib in *BRCA*^{mut} tumours showed there was a relationship between the response in HGOC and 'platinum-sensitivity' of the tumour, as determined by the platinum-free interval before PARP inhibitor therapy (21). It was therefore hypothesised that HGOC that did not have either a germline or somatic *BRCA*^{mut} might also respond to PARP inhibition. In a phase II trial with olaparib 24% (11 out of 46) of patients with HGOC without a

BRCA^{mut} responded (32). Again, most but not all the responses were seen in tumours classified as 'platinum-sensitive'.

The hypothesis was explored further in a randomised phase II trial in which patients with HGOC who responded to platinum-based therapy were randomised to maintenance with olaparib capsules or placebo. The trial explored the concept of using maintenance therapy to improve clinical benefit, determined by prolongation of PFS. A response to platinum-based therapy in patients with recurrent HGOC was used to enrich the population likely to benefit. In 'study 19' 22% were known to have a *BRCA*^{mut}, 14% were *BRCA*^{wt} and 63% had an unknown BRCA status. In this trial the median PFS was prolonged from 4.8 to 8.4 months after the start of trial treatment (HR 0.35 95% CI 0.25-0.49; P < 0.001) (9). Subsequent analysis of *BRCA* status was undertaken in the *BRCA* unknown group and *BRCA* status became available in 96% of the 256 patients enrolled in the trial. The greatest benefit in PFS maintenance with olaparib compared to placebo was seen in the *BRCA*^{mut} group (HR 0.18; 95% CI 0·10–0·31; p<0·0001). However, in the 118 *BRCA*^{wt} patients there was also a significant PFS benefit (HR 0·54; 95% CI 0·34–0·85; p=0·0075) (3). Subsequent phase III trials with the PARP inhibitors, niraparib (NOVA) and rucaparib (ARIEL3) included patients without a *BRCA* mutation and both studies showed significant benefit in the non-*BRCA*^{mut} group (2, 4) (Table1). Both these trials subdivided patients without a *BRCA* mutation in HRD or HRP based on the Myriad or Foundation Medicine HRD assays but these tests were not able to identify sub populations (eg HRP) that did not benefit from maintenance therapy with a PARP inhibitor (2, 4). The false negative rate in this setting, may have been contributed to by the fact that these patients were highly selected for platinum sensitivity, which is in itself a strong marker for HRD. Olaparib, niraparib and rucaparib are now all licensed as maintenance treatment in high grade recurrent ovarian cancers that have responded to platinum-based therapy, irrespective of *BRCA* status and these drugs are now accepted as a standard of care in recurrent ovarian cancer.

First-Line Maintenance Therapy

Recent evidence supports maintenance PARP inhibitor use in the first-line setting following cytoreductive surgery and platinum-based chemotherapy (1, 8, 10, 33). The introduction of olaparib maintenance following chemotherapy in *BRCA*^{mut} ovarian cancer led to an unprecedented improvement with a 70% reduction in the risk of disease progression or death compared to placebo (60 vs 27% HR 0.30, 95% CI 0.23-0.41) (1). Three further randomised phase 3 trials, PRIMA, PAOLA1 and VELIA, have evaluated first-line maintenance PARP inhibitors in *BRCA*^{wt} patients and suggest that *BRCA*^{wt}/HRD tumours may also benefit, although to a lesser degree than the *BRCA*^{mut} population (Table 1) (8, 10, 33). In each of these

trials, BRCA*mut* consistently predicted PARP inhibitor benefit with a similar magnitude to that seen in the relapsed setting (HR range 0.31-0.44) (1, 8, 10, 33).

The PRIMA study compared niraparib and placebo with patients stratified by HRD-score (Myriad). *BRCA*wt /HRD patients benefited from niraparib with a PFS increase from 8.2 to 19.6 months (HR; 0.5, 95% CI 0.31-0.83). The trial was not powered to detect benefit in the HRP subgroup although exploratory analyses indicate some benefit, albeit of a lesser magnitude (HR 0.68; 95%CI 0.49-0.94) (8). The PAOLA-1 study investigated the addition of olaparib or placebo to bevacizumab maintenance (stratified by tumour BRCA status) (10). The HRD score differentiated between *BRCA*^{wt} tumours that derived benefit (HRD HR 0.43; 95% CI 0.28-0.66) and no benefit (HRP HR 0.92; 95% CI 0.72-1.17) from the addition of olaparib (1, 8, 10, 33). In contrast, exploratory analysis within the VELIA study, suggested less benefit in *BRCA*^{wt} tumours from the addition of veliparib given with chemotherapy and as maintenance therapy, whether HRD (HR 0.80; 95%CI 0.64-0.997) or HRP (HR; 0.81; 95% CI 0.6-1.09) (33). Patients were enrolled at diagnosis and not following a selection of patients responding to initial treatment as in PRIMA and PAOLA-1 (1, 8, 10, 33). Secondly, an unvalidated HRD cut off score (Myriad) was used making it harder to draw meaningful conclusions from these data.

PARP inhibitor Monotherapy

Olaparib and rucaparib have monotherapy licences for recurrent *BRCA*^{mut} ovarian cancer with overall response rates (ORR) of 31-41% and up to 53.8% respectively (32, 34-37). Currently there are limited opportunities to use a PARP inhibitors as monotherapy for *BRCA*^{wt} tumours, despite an ORR for olaparib of 24% in *BRCA*^{wt} tumours and 44% for rucaparib in *BRCA*^{wt}/HRD tumours (18, 32) Niraparib is the only drug approved (in the USA) for monotherapy in a heavily pre-treated (≥3 lines) *BRCA*^{wt}/HRD population following an ORR of 24% in the QUADRA trial (38, 39).

Combination therapy

Combining PARP inhibitors with other agents may increase benefit, particularly in non-BRCA or HRP patients. Whilst combining PARP inhibitors with DNA-damaging chemotherapy is appealing due to potential synergy, overlapping toxicity especially myelosuppression, limits this combination (40, 41). More appealing is the combination of PARP inhibitors with other inhibitors of DNA repair, angiogenesis and cell cycle as well as immune checkpoint inhibitors (Tables 1 and 2). These combinations have the potential to increase clinical synthetic lethality, or alternatively act by independent mechanisms without overlapping toxicity. Whilst an in-depth review of PARP inhibitor combination therapy is outside the scope of this review, the

two most evaluated combinations are discussed briefly, and further ongoing studies listed in Table 2.

Preclinical studies suggest that augmentation of hypoxia with drugs such as cediranib may reduce the expression of key HR proteins and sensitise to PARP inhibition, and forms the basis of many ongoing studies (42, 43). The addition of cediranib to olaparib versus olaparib alone in patients with relapsed HGOC increased PFS (17.7 versus 9.0 months) (43), with the greatest benefit in the *BRCA*^{wt} group (23.7 versus 5.7 months) (44). Whether this combination is superior to chemotherapy for recurrent disease is under evaluation (Table 2), and the value of this combination as maintenance therapy is being investigated within ICON9 (NCT03278717). The AVANOVA trial compared niraparib versus niraparib and bevacizumab as a treatment strategy; demonstrating improved PFS in the intention-to-treat population (irrespective of HRD), as well as in the *BRCA*^{wt} group but not the *BRCA*^{mut} group (Table 1) (45).

Preliminary results from early-phase trials demonstrate activity for the combination of PARP inhibitors with immune checkpoint inhibitors, with ORR in HGOC between 18-72% (46, 47). The rationale for this combination is based on two hypotheses. HRD cancers have a higher tumour mutational burden leading to elevated neo-antigen loads, which is thought to stimulate an increased anti-tumour immune response (48, 49). Secondly, treatment with PARP inhibitors upregulates PD-L1 expression *in vivo* and *in vitro* (50), and in the absence of a functional BRCA pathway there is activation of the innate immune response via the STING/TKB1/IRF3 response (51), which may augment the antitumour effect of the combination. The combination of niraparib and pembrolizumab in a predominately platinum-resistant (76%) population was tolerable with an ORR of 18%, with similar ORR regardless of HRD or *BRCA*^{mut} status (Table 1) (47). The ongoing MEDIOLA trial is evaluating olaparib and durvalumab as a chemotherapy sparing regimen for platinum-sensitive recurrent disease in both *BRCA*^{mut} and *BRCA*^{wt} populations. Within the *BRCA*^{mut} cohort, interim results suggest an ORR of 71.9% (95% CI: 53-86) (46). The results in the *BRCA*^{wt} population are awaited and several trials combining PARP inhibitors with immune checkpoint inhibitors are underway (Table 2).

Conclusion

Clinical data supports the use of PARP inhibitor maintenance therapy beyond BRCA^{mut} patients in both the relapsed and first-line setting. In relapsed disease platinum-sensitivity is a good marker for PARP inhibitor response with current HRD assays failing to improve on this, as they do not reliably identify a sub-group of patients who will not benefit. However, as PARP inhibitor therapy use in first-line maintenance setting increases there is an urgent need for

better HRD assays in the BRCA^{wt} population as assessment of platinum-sensitivity may be unclear following complete resection of disease at surgery. HRD tests are needed to help evaluate combination therapies with anti-angiogenic drugs and immune checkpoint inhibitors as platinum-sensitivity assessments may not apply in these patients. However, the molecular and genomic alterations leading to an HRD phenotype are complex, and more research is needed to develop a composite HRD assay to provide a dynamic readout of HRD status.

Key points:

- PARP inhibitors have transformed the management of BRCA^{mut} HGOC.
- Clinical data demonstrates that this benefit extends beyond BRCA^{mut} cancers, particularly in those cancers characterised by homologous recombination deficiency.
- A variety of strategies exist to select *BRCA*^{wt} tumours who are most likely to benefit from PARP inhibition can these can be grouped into one of four categories: clinical; functional; sequence/epigenetic and DNA 'scarring' assays.
- Whilst currently available HRD assays predict the magnitude of benefit from PARP inhibitors, they consistently fail to identify a sub-group of patients who will not benefit.
- Ongoing research is required to develop a composite HRD assay which provides a dynamic readout of HRD status and allows stratification of patients to maximise benefit from PARP inhibitor treatment.

Figure and Table Legends

Figure 1: Targets of genomic disruption related to homologous recombination deficiency. Other RAD family members include genes such as RAD52 and RAD54L. Other FANC family members encode other subunits of the Fanconi Anaemia core complex, and related proteins.

Figure 2: Onion plot showing molecular subgroups of HGSOC. Core: ubiquitous p53 inactivation. Layer 1: homologous recombination proficient tumours, including CCNE1 amplified cases. Layer 2: homologous recombination deficient tumours. Outer layer: tumour suppressor genes frequently inactivated by structural variants.

Table 1: Key randomised controlled trials of PARP inhibitor maintenance therapy and combination therapy in HGOC. Benefit from PARP inhibitor is displayed as progression free survival (PFS) or overall response rate (ORR) with corresponding hazard ratios (HR) and 95% confidence intervals (CI). Primary analyses are in black font with exploratory analyses in grey. Key: HRD = homologous recombination deficiency, BRCAmut = mutation in *BRCA1* or *BRCA2*

gene, BRCAwt = BRCA1 /2 wild-type, g = germline, ITT = intention to treat, LOH – loss of heterozygosity score, NR = not reached.

Table 2: **PARP inhibitor combination trials in progress.** Key: HRD = homologous recombination deficiency, BRCAmut = mutation in *BRCA1* or *BRCA2* gene, BRCAwt = BRCA1 /2 wild-type, ATMmut = mutation in ATM, SOC = standard of care

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Conflicts of interest

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	NCT number and Trial Name
Anti-angiogenesis	NCT02446600 NRG-GY004
	NCT02502266 NRG-GY005
	NCT03117933 OCTOVA
	NCT03278717 ICON9
	NCT03326193 OVARIO
Immune Check-Point Inhibitors	NCT02734004 MEDIOLA
	NCT03330405 JAVELIN MEDALY
	NCT03101280 COUPLET
	NCT03522246 ATHENA
	NCT03737643 DUO-O
	NCT03602859 FIRST

PARP inhibitor	Combination	Comparator
olaparib	cediranib	olaparib single agent vs carboplatin based chemotherapy
olaparib	cediranib	olaparib single agent vs SOC chemotherapy
olaparib	cediranib	olaparib single agent or weekly paclitaxel chemotherapy
olaparib	cediranib	olaparib
niraparib	bevacizumab	NA
olaparib	durvalumab	NA
talazoparib	avelumab	NA
rucaparib	atezolizumab	NA
rucaparib	nivolumab	rucaparib/nivolumab vs rucaparib/placebo vs placebo/nivolumab vs placebo/placebo
olaparib	durvalumab	Maintainence therapy: bevacizumab/placebo/placebo vs bevacizumab/durvalumab/placebo vs bevacizumba/durvalumab/olaparib
niraparib	dostarlimab	Maintainence therapy: placebo/placebo vs niraparib/placebo vs niraparib/dostarlimab +/- bevacizumab as SOC

Indication	Patient population	Phase
platinum sensitive disease	Any BRCA/HRD	3
platinum resistant disease	Any BRCA/HRD	3
platinum resistant disease	Any BRCA/HRD	2
maintenance following response to platinum chemotherapy for relapsed disease	Any BRCA/HRD	3
maintenance following first line chemotherapy	high grade serous or BRCAmut	2
platinum sensitive	BRCAmut and BRCAwt cohorts	2
platinum sensitive	BRCAmut or ATMmut	2
platinum sensitive	Any BRCA/HRD	1 and 2
maintenance following first line chemotherapy	Any BRCA/HRD	3
durvalumab/placebo with concurrent chemotherapyand bevacizumab followed by maintenance therapy first line	Any BRCA/HRD	3
dostarlimab/placebo with concurrent chemotherapy followed by maintenance therapy first line	Any BRCA/HRD	3

Study
Maintenar
ARIEL3 (NCT01968213) Coleman et al. Lancet, 2017
NOVA (NCT01847274) Mirza et al. NEJM, 2016
SOLO2 (NCT01874353) Pujade Lauraine, Lancet Oncology, 2017
Study19 (NCT00753545) Ledermann et al. Lancet Oncol, 2014
PAOLA-1 (NCT02477644) Ray-Coquard et al. Annals of Oncology, 2019
PRIMA (NCT02655016) Gonzalez-Martin, NEJM, 2019
VELIA (NCT0247058) Coleman et al, NEJM, 2019

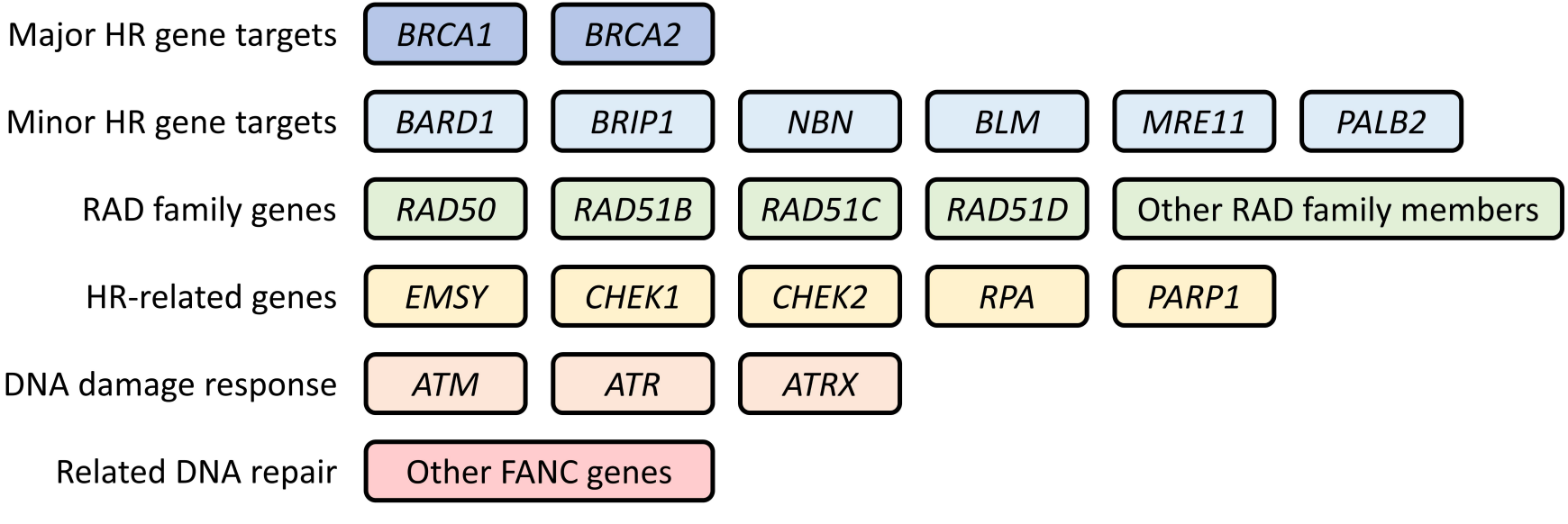
SOLO1 (NCT01844986) Moore et al.NEJM, 2018
AVANOVA (NCT02354131) Mirza et al. Lancet Oncology , 2019
NCT0111648 Liu et al. Annals of Oncology 2019
TOPACIO (NCT02657889) Konstantinopoulos et al. JAMA Oncology , 2019

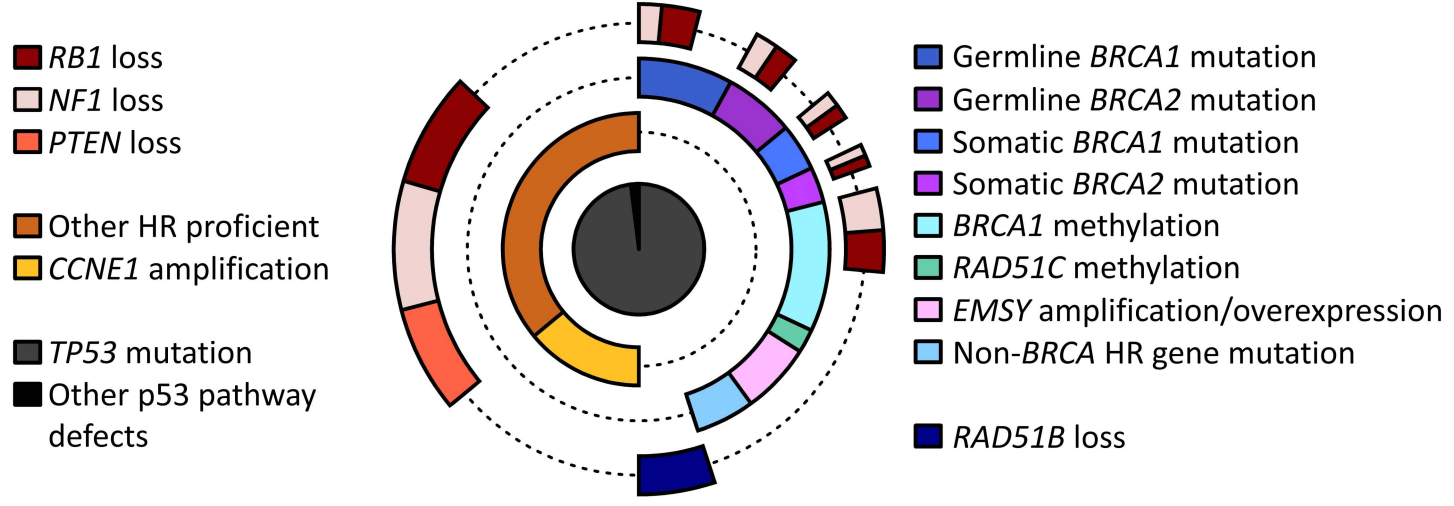
Drug	Primary outcomes	PFS (months) PARP inhibitor v placebo
ıce Therapy in Platinum Sensitive Reccurence (>=2 previous lines of platinum based chemot		
Rucaparib 600mg bd (n=375) v placebo (n=189)	PFS in ITT, HRD (LOH) and BRCAmut group	All patients: 10.8 v 5.4
		BRCAmut: 16.6 v 5.4
		HRD: 13.6 v 5.4
		HRD & BRCAwt: 9.7 v 5.4
		HRP: 6.7 v 5.4
Niraparib 300mg od (n=372) v placebo (n=181)	PFS according to BRCAmut status and HRD status (Myriad)	gBRCAmut: 21 v 5.5
		gBRCAwt: 9.3 v 3.9
		HRD & BRCAwt: 12.9 v 3.8
		HRP: 6.9 v 3.8
Olaparib 300mg bd tablets (n=196), placebo (n=99)	PFS	BRCAmut: 19.1 v 5.5
Olaparib 400mg bd capsules (n=136), placebo (n=129)	PFS analysed by overall population and BRCA status	All patients: 10.8 v 5.4
		BRCAmut: 11.2 v 4.3
		BRCAwt 7.4 v 5.5
Maintenance PARP inhibitor - first-line setting		
Olaparib 300mg bd tablets(n=537) plus bevacizumab (15mg/kg d1, q3w) v placebo (n= 269) plus bevacizumab	PFS in ITT population	All patients: 22.1 v 16.6
		BRCAmut: 37.2 v 21.7
		BRCAwt: 18.9 v 16
		HRD: 37.2 v17.7
		HRD/BRCAwt: 28.1 v 16.6
		HRP/uk: 16.9 v 16
Niraparib 300mg (n=487) v placebo (n=246)	PFS in ITT and HRD	All patients: 13.8 v 8.2
		HRD: 21.9 v 10.4
		HRD/BRCAmut: 22.1 v 10.9
		HRD/BRCAwt: 19.6 v 8.2
		HRP: 8.1 v 5.4
carboplatin/taxane + maintenance placebo (n=375), carboplatin/taxane and maintenance veliparib (n=383) carboplatin/taxane with veliparib and maintenance veliparib (n=382)	PFS in veliparib throughout group v control group in ITT, BRCAmut and HRD	All patients: 23.5 v 17.3
		BRCAmut: 34.7 v 22
		HRD: 31.9 v 20.5
		BRCAwt: 18.2 v15.1
		HRP: 15.0 v 11.5

Olaparib 300mg bd tablets (n=260), placebo (n=131)	PFS in ITT population	BRCAmut: NR v 13.8
Combination Studies		**PFS (months) Combination therapy v PARP inhibitor**
Niraparib 300mg + bevacizumab 15 mg/kg (n=48) v Niraparib 300mg (n=49)	PFS in ITT population	All patients: 11.9 v 5.5
		BRCAmut: 14.4 v 9.0
		BRCAwt: 11.3 v 4.2
		HRD & BRCAwt: 11.9 v 4.1
cediranib 30 mg daily and olaparib capsules 200 mg (n=44) v olaparib capsules 400 mg bd (n=46)	PFS in ITT population	All patients: 16.5 v 8.2
		BRCAmut: 16.4 v 16.5
		BRCAwt: 11.3 v 4.2
		ORR
Niraparib 200mg + Pembrolizumab 200mg IV (n=62) [single arm study]	ORR in ITT population	All patients: 18%
		HRD: 14%
		HRP 19% BRCAmut 18% BRCAwt 19%

HR (95% CI)
therapy)
0.36 (0.3-0.45)
0.23 (0.16-0.34)
0.32 (0.24-0.42)
0.44 (0.29-0.66)
0.58 (0.4-0.85)
0.27 (0.17-0.41)
0.45 (0.34-0.61)
0.38 (0.24-0.59)
0.58 (0.36-0.92)
0.33 (0.24-0.44)
0.35 (0.25-0.49)
0.18 (0.34-0.85)
0.54 (0.34-0.85)
0.59 (0.49-0.72)
0.31 (0.20-0.47)
0.71 (0.58-0.88)
0.33 (0.25-0.45)
0.43 (0.28-0.66)
0.92 (0.72-1.17)
0.62 (0.50-0.76)
0.43 (0.31-0.59)
0.40 (0.27-0.62)
0.50 (0.31-0.83)
0.68 (0.49-0.94)
0.68 (0.56-0.83)
0.44 (0.28-0.68)
0.57 (0.43-0.76)
0.80 (0.64-0.997)
0.81 (0.60-1.09)

0.30 (0.23-0.41)
HR (95% CI)
0·35 (0·21–0·57)
0.49 (0.21-1.15)
0.32 (0.17-0.58)
0.19 (0.06-0.59)
0.50 (0.30-0.83)
0.76 (0.38-1.49)
0.31 (0.15-0.66)
95% CI
95% CI 11-29
95% CI 4-33
95% CI 9-34
95% CI 3-47
95% CI 10-31


Major HR gene targets
BRCA1
BRCA2
Minor HR gene targets
BARD1
BRIP1
NBN
BLM
MRE11
PALB2
RAD family genes
RAD50
RAD51B
RAD51C
RAD51D
Other RAD family members
HR-related genes
EMSY
CHEK1
CHEK2
RPA
PARP1
DNA damage response
ATM
ATR
ATRX
Related DNA repair
Other FANC genes


RB1 loss
NF1 loss
PTEN loss
Other HR proficient
CCNE1 amplification
TP53 mutation
Other p53 pathway defects
Germline *BRCA1* mutation
Germline *BRCA2* mutation
Somatic *BRCA1* mutation
Somatic *BRCA2* mutation
BRCA1 methylation
RAD51C methylation
EMSY amplification/overexpression
Non-*BRCA* HR gene mutation
RAD51B loss